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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/513,362 | 02/25/2000 | Mark S Chee | A-67851-2/DJB/RMS/DCF | 7034 |

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| EXAMINER | |
|---|---|
| STRZELECKA, TERESA E | |
| ART UNIT | PAPER NUMBER |
| 1637 | |

DATE MAILED: 06/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/513,362 | CHEE ET AL. | |
| | Examiner | Art Unit | |
| | Teresa E. Strzelecka | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/16/05;5/3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 16, 2005 has been entered.

2. Claims 1-34 were previously pending. Applicants did not amend any claims. Claims 1-34 are pending and will be examined.

3. All previously made rejections are maintained for reasons given in the "Response to Arguments" section below.

### *Information Disclosure Statement*

4. The information disclosure statements (IDS) submitted on February 16, 2005 and May 3, 2005 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

### *Response to Arguments*

5. Applicant's arguments filed July 22, 2004 have been fully considered but they are not persuasive. The arguments were considered in an Advisory Action mailed August 13, 2004 and are repeated below.

A) Regarding the rejection of claims 1-4, 6-10, 12-17 and 22-27 under 35 U.S.C. 103(a) over Navot et al. and Walt et al., Applicants argue that Navot et al. do not teach large scale sequence determination involving a plurality of target nucleic acids, and that there is no motivation to combine Navot et al. and Walt et al. Further, Applicants argue that "Establishing that the prior art

would have suggested the claimed method requires an underlying factual showing of a suggestion, teaching, or motivation to combine the prior art references and is an "essential evidentiary component of an obviousness holding." *Brown & Williamson Tobacco*, 229 F.3d at 1124-25 (*quoting C.R. Bard, Inc. u 513 Sys., Inc,* 157 F.3d 1340, 1351-52 (Fed.Cir.1998); *see also C.R. Bard* at 1351 (obviousness requires some suggestion, motivation, or teaching in the prior art where to select the components that the inventor selected and use them to make the new device; *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000) (there must be some motivation, suggestion or teaching in the prior art of the desirability of making the specific combination that was made by the applicant). The evidentiary showing must be clear and particular and broad conclusory statements about the teachings of the cited references, standing alone, are not "evidence." *Brown & Williamson Tobacco*, 229 F.3d at 1125 (quoting *In re Dembiczak*, 175 F.3d 994, 1000 (Fed.Cir.1999), abrogated on other grounds by *In re Gartside*, 203 F.3d 1305, 53 USPQZd 1769 (Fed.Cir.2000)).

However, as noted in the previous office actions, there is a perfectly valid motivation to combine the two references. In this case, Navot et al. teach pyrosequencing of nucleic acids which may be attached to microbeads in an electrophoresis-free system, and attachment to the solid support provides confinement to the sample (col. 15, lines 1-14), and Walt et al. teach microbeads with attached nucleic acids, distributed randomly on the surface of the fiber optic bundle, creating an microbead array (col. 3, lines 35-45; col. 4, lines 35-38; col. 8, lines 15-19; col. 9, lines 41-67; col. 10, lines 1-47). Both references teach microbeads, and Walt et al. teaches an efficient and inexpensive way of creating an array (col. 4, lines 53-58). Therefore, provided with the teachings of Navot et al. and Walt et al., a skilled artisan would be motivated to use the microbead array of Walt et al. to detect the microbead sequencing reactions of Navot et al. Further, the paragraph from Walt et al. cited by Aplicants (col. 4, lines 44-59) provides additional support for the motivation to

use the references, since Walt et al. teach synthesis of bioactive agents, which is what DNA sequencing is. As can be seen from the previous office actions and responses to arguments provided, the statements about motivation are supported by clear factual showing of the motivation present in both references, and are not simply broad, conclusory statement.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Applicants further bring on the argument about the lack of factual support for the motivation, which was addressed above. The rejection is maintained.

B) Regarding the rejection of claims 5 and 11 (claim 33 was also included in this rejection, but Applicants do not mention it) under 35 U.S.C. 103(a) over Navot et al. and Walt et al., further in view of Balch et al., Applicants argue that there was no motivation to combine Navot et al. and Walt et al. This argument was addressed above.

The rejection is maintained.

C) Regarding the rejection of claims 18-21 and 28-30 under 35 U.S.C. 103(a) over Navot et al. and Walt et al., further in view of Nyren et al., Applicants argue that there is no motivation to combine the kit components of two different references. As stated in the previous office actions, the kits were conventional in the field of molecular biology at the time of the invention and provided convenience and cost-effectivness for practicioners in the art. Further, both Navot et al. and Nyren et al. teach pyrosequencing and pyrosequencing kits, with Navot et al. teaching a kit

comprising primers and DNA polymerase (col. 6, lines 63-67; col. 7, lines 1-10; col. 9, lines 5-7), and Nyren et al. teach a kit comprising a sequencing primer, a polymerase, a detection enzyme means for identifying pyrophosphate release, dNTPs or ddNTPs (page 20, second paragraph; page 21, first paragraph). Therefore, as can be seen from these two references, there is a strong motivation to combine different reaction components into kits. Since strong motivation exists to combine Walt et al. with Navot et al., it would have been obvious to add components of the array of Walt et al. to the kit (see also MPEP 2144).

## 2144 Sources of Rationale Supporting a Rejection Under 35 U.S.C. 103

**RATIONALE MAY BE IN A REFERENCE, OR REASONED FROM COMMON KNOWLEDGE IN THE ART, SCIENTIFIC PRINCIPLES, ART RECOGNIZED EQUIVALENTS, OR LEGAL PRECEDENT**

The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also *In re Kotzab,* 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning).

The rejection is maintained.

### *Claim Rejections - 35 USC § 103*

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-4, 6-10, 12-17, 22-27 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Navot et al. (U.S. Patent No. 6,335,165 B1; cited in the previous office action) and Walt et al. (U.S. Patent No. 6,327,410 B1; cited in the previous office action).

A) Navot et al. teach a method of sequencing GC-rich regions of nucleic acids, the method comprising contacting modified GC-rich nucleic acid with a sequencing primer, synthesizing a complementary strand in a stepwise manner, in which an identity of each incorporated nucleotide is determined, and determining the sequence of the GC-rich nucleic acid (col. 7, lines 10-29; col. 12, lines 34-46). The nucleotide addition is catalyzed by a DNA polymerase (the first enzyme) (col. 14, lines 46-67). Navot et al. teach amplification of genomic DNA (col. 6, lines 53-58; col. 18, lines 37-40).

The identity of each incorporated oligonucleotide can be determined by monitoring a release of a pyrophosphate (PPi) group and the detection of PPi is achieved enzymatically. The PPi formed in the sequencing reaction is converted to ATP by ATP sulfurylase (second enzyme) and the ATP production is monitored by the firefly luciferase (third enzyme) (col. 7, lines 60-67; col. 4, lines 55-67; col. 5, lines 1-36; col. 12, lines 66-67; col. 13, lines 1-35).

Another way of determining the identity of an incorporated nucleotide is achieved by using nucleotide analogs, which include a removable blocking group at the 3'-OH position and a removable reporter group. Following the addition of a nucleotide to the complementary strand the blocking group is removed to permit the addition of the next nucleotide. The removable reporter group allows identification of the incorporated nucleotide (col. 13, lines 43-67).

The target nucleic acid can be bound to a solid support either directly or indirectly, for example, through a capture probe (col. 10, lines 29-33). In another embodiment, either the sequencing primer or the target can be immobilized on beads (col. 15, lines 1-14).

Navot et al. teach a kit comprising amplification primers and a DNA polymerase (col. 6, lines 63-67; col. 7, lines 1-10; col. 9, lines 5-7).

B) Navot et al. do not teach microspheres (beads) randomly distributed on a surface of a substrate, where the substrate comprises discrete sites, and the discrete sites are wells. They do not teach the substrate being a fiber optic bundle.

C) Walt et al. teach microsphere-based analytical chemistry system in which the microspheres are distributed on a substrate which might be a fiber optic bundle (Abstract). The surface of the substrate comprises discrete sites into which at least two subpopulations of microspheres are distributed. Each of the microspheres comprises a bioactive agent and an optical signature which allows identification of the bioactive agent. The beads can be randomly distributed on the array (col. 3, lines 35-45; col. 4, lines 35-58). The bioactive agent attached to the microsphere can be a nucleic acid, particularly a nucleic acid probe (col. 8, lines 15-19; col. 9, lines 41-67; col. 10, lines 1-47). The array can be used for sequencing (col. 24, lines 51-52).

The substrate materials include glass, plastics and a variety of other materials. The surface of the substrate contains discrete sites, which might be wells, and the substrate may be a fiber optic bundle (col. 5, lines 32-46, lines 61-67; col. 6, lines 22-41).

Walt et al also teach a composition comprising a substrate with discrete sites (wells) and a population of microspheres randomly distributed in the wells, the microspheres comprising a bioactive agent (claims 1, 5, 9, 27 and 39).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used microspheres randomly distributed on a substrate of Walt et al. as the beads in the pyrosequencing method of Navot et al. The motivation to do so, expressly provided by Walt

et al., would have been that synthesis of nucleic acids was separated from their placement on the array and random distribution of beads was fast and inexpensive.

8. Claims 5, 11 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Navot et al. and Walt et al. as applied to claims 1 and 10 above, and further in view of Balch (U.S. Patent No. 6,083,763; cited in the previous office action).

A) Claim 5 is drawn to the hybridization complexes comprising target sequences, sequencing primers, adapter probes and capture probes covalently attached to the microspheres. Claim 11 is drawn to a hybridization complexes comprising capture probes. Claim 33 is drawn to a method of claim 11 where the hybridization complexes comprise adapter probes.

B) Neither Navot et al. nor Walt et al. teach adapter probes.

C) Balch teaches molecular analysis aparatus for high-throughput analysis of molecular targets in complex mixtures. This apparatus can be used for DNA amplification and sequencing in an array format. (Abstract, Example III). Each location of the array comprises a capture probe attached to a solid substrate (col. 17, lines 28-41; col. 18, lines 55-66). The target probes (adapter probes) are designed to be complementary to both the capture probes and the target nucleic acids (col. 20, lines 39-49; Fig. 5a). The capture probes can be used directly to form hybridization complexes with the target nucleic acid sequences (col. 21, lines 21-23).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the adapter probes of Balch for the formation of primer-target complexes in the combined method of Navot et al. and Walt et al. The motivation to do so, expressly provided by Balch, would have been that adapter probes a delivered unique binding domain for each site on an array.

9. Claims 18-21 and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Navot et al. and Walt et al. as applied to claims 1 and 10 above, and further in view of Nyren et al. (WO 98/13523; cited in the previous office action).

A) Claims 18-21 are drawn to a kit for nucleic acid sequencing comprising a substrate with discrete sites, population of microspheres randomly distributed in these sites, the microspheres comprising capture probes, an extension enzyme, dNTPs, a second enzyme for conversion of PPi to ATP, a third enzyme for the detection of ATP, and dNTPs with different labels.

B) Navot et al. teach a kit as described above, but does not teach a substrate with discrete sites, population of microspheres randomly distributed in these sites, the microsphres comprising capture probes, dNTPs, a second enzyme for conversion of PPi to ATP, a third enzyme for the detection of ATP, and dNTPs with different labels. Walt et al also teach a composition comprising a substrate with discrete sites (wells) and a population of microspheres randomly distributed in the wells, the microspheres comprising a bioactive agent (claims 1, 5, 9, 27 and 39), but does not teach dNTPs, a second enzyme for conversion of PPi to ATP, a third enzyme for the detection of ATP, and dNTPs with different labels.

C) Nyren et al. teach a kit comprising a sequencing primer, a polymerase, a detection enzyme means for identifying pyrophosphate release, dNTPs or ddNTPs (page 20, second paragraph; page 21, first paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have added kits of Nyren et al. to a kit and a composition disclosed by Navot et al. and Walt et al. The motivation to do so would have been that kits were conventional in the field of molecular biology and provided the benefits of convenience and cost-effectiveness for practitioners in the art.

10. No claims are allowed.

***Conclusion***

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
5/20/05

JEFFREY FREDMAN
PRIMARY EXAMINER
5/20/05